REMARKS

Status Of The Claims

Claims 1-80 were filed. Claims 1-44 (Group I) were elected pursuant to a restriction requirement, leaving claims 45-80 withdrawn from consideration. Claims 1-4 and 32-44 (Species E and associated linking claims) were elected pursuant to an election of species requirement, leaving claims 5-31 also withdrawn from consideration. All of these claims are the subject of the rejection currently outstanding in the application.

Rejections Under 35 USC §112, First Paragraph

The Examiner rejected claims 1-4 and 32-44 under 35 USC §112, first paragraph, for lack of enablement. Specifically, the Examiner acknowledged that the specification enables the protection of tissue from oxidative stress induced by heme/peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD). The rejection is for insufficient enablement for the protection of all tissue types from oxidative stress not induced by free radicals or an agent that is capable of generating free radicals. Similarly, the Examiner also particularly noted claims 34-36 on the basis that the specification does not enable protection of tissue in subjects suffering from the compilation of diseases listed in those claims.

In response, the applicants believe that that various specification passages and Examples provide adequate guidance linking the diseases to the to the claimed compounds, protection of tissue components by such compounds based on the mechanisms disclosed and tested by the inventors, and a reasonable amount of data showing the efficacy of the invention for various numbers of phosphorus atoms.

This is because there is no lack of enablement in the specification for combinations or compounds that are reasonably within the scope of the disclosure, solely because less than all possible combinations and compounds have been specifically tested. "The fact that some experimentation is necessary does not preclude enablement." *PPG Industries v. Guardian Industries Corp.*, 75 F.3d 1558, 37 USPQ2d 1619 (Fed. Cir. 1996). Indeed, "a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question

provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable determination of how to practice a desired embodiment of the invention claimed." *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. 1982).

In the pending application, specification page 16, lines 1-8 describes various diseases or disorders that relate to or are caused at least in part by dysfunction, alteration or loss of one or more G-protein coupled receptors); page 16, lines 14-20 describes how muscarinic receptors are G-protein coupled receptors, which express throughout various tissues. Such disclosure in the specification provides more than "a reasonable amount of guidance" to proceed beyond the specific examples and models. The Examiner acknowledges that the heme/peroxide and low molecular weight inhibitors in patients with Alzheimer's disease is a model, and the specification clearly sets forth the basis by which that model is enabling for combinations not specifically tested, thus providing an enabling disclosure. Therefore, the Examples and results illustrated in Figures 1-7, along with Formulas I and II (specification pages 21-22), provide the person of ordinary skill with adequate enablement of the invention.

Finally, the Examiner also rejected claims 1-4 and 32-44 under 35 USC §112, first paragraph, for lack of enablement, specifically for phosphorylated compounds having three or more phosphorus atoms. This rejection is not appropriate for claim 32, which is specifically drawn to the compounds acknowledged by the Examiner to be disclosed in the written description (and now, by amendment, including tripolyphosphate as noted by the Examiner and specifically noted in Figure 7 along with specification page 36, line 10 and page 38, lines 1-2). Claim 33 depends on claim 32 and is similarly limited. As for the other claims, the general comments above regarding undue experimentation apply to this rejection as well.

Rejections Under 35 USC §112, Second Paragraph

The Examiner rejected claims 1-4 and 32-44 under 35 USC §112, second paragraph, for indefiniteness, for a variety of reasons. Claim 1 was noted because of the use of the term "tissue component." In response, the Examiner's attention is respectfully directed to page 10, lines 22-23 of the specification, in which the term "tissue component" is specifically defined for purposes of the invention. Claims using terms defined in the specific context of the invention are definite,

because they set out the metes and bounds of the invention to the person of ordinary skill in the art. Also, please note page 1, line 22 to page 2, line 8, in which the context of carbohydrates, the specific component discussed by the Examiner, is described. The claimed compounds perform their claimed functions without necessarily interacting directly with the receptor, but it is clear from the specification and the knowledge of the art that they may interact with agents causing damage to receptors, *e.g.*, with compounds that oxidize carbohydrates. Protection of carbohydrates by prevention of oxidation is a method of protecting the cellular function involving such carbohydrates. Similar reasoning applies to proteins (which are known to be oxidized in Alzheimer's patients), and nucleic acids, other tissue components identified by the specification.

The standard to comply with 35 USC § 112, second paragraph is very clearly known: "The requirement that the claims 'particularly point[] out and distinctly claim[]' the invention is met when a person experienced in the field of the invention would understand the scope of the subject matter that is patented when the claim is read in conjunction with the rest of the specification. 'If the claims when read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, §112 demands no more.'" *S3 Incorporated v. Nvidia Corporation*, 259 F.3d. 1364, 1367, 59 USPQ2d 1745, 1747 (Fed. Cir. 2001), *quoting Miles Laboratories, Inc. v. Shandon*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993); *citing Union Pacific Resources Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 692, 57 USPQ2d 1293, 1297 (Fed. Cir. 2001); *North American* Vaccine, *Inc. v. American Cyanamid Co.*, F.3d 1571, 1579, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993); *Hybritech, Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1986).

The Examiner argues that "in the absence of the specific moieties intended to be protected as claimed, the term 'tissue component' renders in the claims in which it appears indefinite in all occurrences wherein Applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language the particular moieties Applicant regards as those which will be protected by the composition matter claimed." (Page 8.) In this application, the scope of the invention claim language can easily be understood by the person of ordinary

skill based on the specifically defined meaning of the disputed claim term, especially when read in light of the written description.

Claims 1-4 and 32-44 were noted because "alphabetic variables with alternative definitions within the same claim renders the claims in which such situation appears indefinite." Claim 1 (at lines 6 and 10) and claim 4 have been amended to use primed variables (X' and n'). The specification has not been amended in every instance because the applicants believe that the burden to do so would be greater than is justified because of the public record provided by the prosecution history, and the ability of the ordinarily skilled artisan to interpret the claims in light of the specification despite the use of only unprimed variables in the specification. An omnibus statement to that effect is added at the end of the specification by amendment above.

Claims 34-36 were noted for the use of the term "subject" because of insufficient antecedent basis in claim 4 for the term. Claim 4 has been amended to provide such basis.

Claims 34-36 were also noted because they recite various diseases, but depend upon claims 1 and 4 which are directed to protection of tissue components and tissue, respectively. In response, the applicants believe that there is sufficient antecedent basis for the limitations of the dependent claims because they limit the scope of the previously recited environment of the invention, *i.e.*, they narrow the scope of the "patient in need" recited in each independent claim, by limiting those independent claims to a patient suffering from the recited diseases.

Rejections Under 35 USC §103(a)

The Examiner rejected claims 1-4 and 32-44 under 35 USC §103(a) as obvious over Venters, Jr. *et al.* in view of entries 3908 and 7135 of the Merck Index.

All of the rejections should be withdrawn because neither reference, either alone or in combination with any other relevant reference, provides any suggestion or motivation for the ordinary artisan to make the combination of teachings asserted by the Examiner; nor is there any reasonable expectation of success should the combination nonetheless be made. Therefore, a *prima facie* case for obviousness under 35 USC §103(a) has not been made.

There are several perspectives on the Examiner's reasoning that are persuasive of non-obviousness. First, Venters *et al.* simply identify EDTA as a "metal chelator" (Abstract, lines 6-7; page 98, column two, Section 4., first paragraph, lines 4-5), which is at best only a non-enabling statement because Venters *et al.* do not even speculate, much less prove, that the protective action of EDTA is due to its ability to bind or chelate metals. Absent such foundation for the technical basis for the Examiner's position, it cannot be said that the legal requirements for obviousness have been established.

Second, and highly persuasive of non-obviousness, is the common-sense observation that heme is a compound that is *already* chelated, *i.e.*, heme contains a porphyrin chelating agent bonded to an iron (II) atom. The Examiner has not provided any reasoning, based on the prior art as opposed to the applicant's own disclosure, as to why a person of ordinary skill would be motivated to chelate a compound that is already chelated; and, in particular, the Examiner has not shown that there would be any reasonable expectation of success to do so with the compounds cited by the Examiner.

Third, while Venters *et al.* show that heme oxygenase-1 protects the human brain muscarinic receptor from inactivation, this enzyme is well known to *release* iron from heme. ("Via oxidation, HO cleaves the α-meso carbon bridge of b-type heme molecules to yield equimolar quantities of biliverdin IXa, CO, and free iron." Otterbein *et al.*, Am J Physiol Lung Cell Mol Physiol 279: L1029-L1037, 2000, at L1029, column two, first paragraph.)[1] This knowledge does not support the theory that protection is due to chelation of metal, in fact it is contrary to it. At a minimum, a rejection for obviousness requires consideration of the prior art read as a whole. "A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02, *citing W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). And, even more to the point, "the totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of

[1] A copy of this reference will be cited in an Information Disclosure Statement to be filed in the application, or it may be found at http://ajplung.physiology.org/cgi/reprint/279/6/L1029.pdf (accessed November 13, 2003).

nonobviousness. MPEP § 2145 X. D. 3., *citing In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Fourth, Venters *et al.* state only that "these antioxidants may function to protect the integrity of the mAChR in vivo..." Venters *et al.* do not provide any teaching or suggestion that other antioxidants such as bioflavonoids can or will do so. Again, the person of ordinary skill in the art would not be motivated to combine the teaching of Venters *et al.* with any other reference to achieve the claimed invention, as required to support a rejection for obviousness.

Taken as a whole, the limited teachings of the Venters *et al.* reference weigh strongly in favor of concluding that the claims are patentable under 35 USC §103(a).

Conclusion

For the reasons given above, Applicants submit that the amended claims should be allowed. The applicants are very open to authorizing by telephone any Examiner's Amendments that would address whatever issues may remain in the application.

If you have any questions, please contact me at your convenience by telephone to advance prosecution in any manner possible.

Very truly yours,

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